

REMARKS/ARGUMENTS

With entry of this amendment, claims 121-145 are pending. Claims 121 and 122 are amended. Claims 121 and 122 are amended to clarify that vector comprises an adenovirus left inverted terminal repeat sequence; an adenovirus packaging sequence; a first adenoviral-associated inverted terminal repeat sequence; a first inverted repeat sequence; a heterologous promoter sequence which mediates transcription; a foreign gene sequence; a second inverted repeat sequence; a second adenoviral-associated inverted terminal repeat sequence; a nucleotide sequence that mediates replication of an adenovirus in a transduced cell; and an adenovirus right inverted terminal repeat sequence; wherein the adenovirus packaging sequence is located on the parallel strand of the vector; and wherein the anti-parallel strand comprises a nucleotide sequence encoding a modified adenoviral fiber protein which alters the tropism of the adenovirus vector, and wherein the modified adenoviral fiber protein is a modified fiber knob, a modified fiber tail or a modified fiber shaft. Support for this claim amendment is provided in the specification, for example, at page 21, lines 24-29; page 23, line 30 to page 24, line 4; and page 19, lines 24-29. Claims 121 and 122 are also amended to change the word "step" to "part." Claim 143 is amended to correct a minor error. No new matter is added by these amendments. No claim amendment should be construed as acquiescence in any ground of rejection.

Specification

The specification is objected to as allegedly informal. In particular, the Examiner objects that at page 86, line 15, " β -gal" is written as " \square gal." Applicants have submitted a replacement paragraph which corrects this typographical error and other typographical errors. No new matter is added by these amendments.

The text in the same paragraph is also objected to because the Examiner alleges it references Figure 17 but does not describe that figure. Applicants respectfully traverse this objection. Figure 17 is cited to illustrate the mechanism by which the vector pAd.AAV-BG can be prepared. Figure 17 is described in the Brief Description of the Figure at page 10, lines 14-21.

To expedite prosecution, Applicants have amended the legend for Figures 17A and 17B to more fully describe the two recombination mechanisms shown. Support for the amended description of Figures 17A and 17B is provided in the figure itself. Applicants have further amended the paragraph beginning at page 86, line 15, to include cross-references to plasmids pCD1 and pAd5fiberX, portions of which are shown in Figure 9. No new matter is added by these amendments.

Applicants therefore request the Examiner withdraw this objection.

Drawing

Applicants also submit herewith revised Figures 17A and 17B. In comparing the informal Figures 17A and 17B with formal Figures 17A and B, certain differences were noted. While Applicants do not believe these differences introduce new matter, Applicants have revised formal Figures 17A and 17B. A marked up copy of Figures 17A and 17B is also enclosed.

Oath/Declaration

The declaration was objected to for the reasons set forth in the Jan. 16, 2004 office action. Applicants submit herewith a substitute declaration.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 121-145 stand rejected as allegedly lacking enablement for a nucleotide sequence encoding a modified adenoviral fiber protein on the anti-parallel strand of the recombinant double-stranded adenovirus vector. The Examiner acknowledges the specification provides guidance for the generation of hybrid adenoviral vectors that have AAV ITR sequences and foreign genes under control of heterologous promoters inserted into an adenoviral vector and for alteration or modification of fiber proteins.

Applicants respond to the Examiner's modified rejection in the instant office action. The Examiner says, *inter alia*, the claims are not enabled. The Examiner reason the art does not recognize a gene encoding the fiber as being on the anti-parallel strand.

Applicants respectfully disagree that the claims are not enabled. Applicants' claims are directed to a recombinant adenovirus vector which includes certain recited elements, including a nucleotide sequence on the anti-parallel strand that encodes a modified adenoviral fiber protein which alters the tropism of the adenovirus vector. Applicants submit that prior recognition of the fiber gene on the parallel strand does not preclude enablement of the instant claims, for the reasons discussed below.

The Examiner also says the fiber gene on naturally occurring adenoviruses is on the "r" strand. Therefore, the Examiner argues it would be difficult to invert the fiber coding sequences without upsetting the temporal and spatial arrangement of the surrounding genes.

Applicants respectfully disagree. The fiber coding sequence in its native location is not essential for expression of the surrounding genes. For example, Legrand et al. (J. Virol. 73:907-919 (1999), submitted with the information disclosure statement dated April 24, 2002) showed that the fiber coding sequence can be deleted. The fiber-deleted virus did not produce viral plaques in the absence of fiber protein. *Id.* at 909. However, when the fiber protein was provided in *trans*, plaques were formed. The authors explained this difference by noting that the viral DNA could be packaged in the absence of fiber protein, but capsids missing fiber protein could not infect cells. *Id.* at 917. Thus, the absence of fiber coding sequences did not prevent replication or packaging.

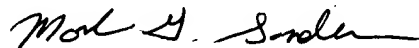
Applicants also refer the Examiner to an article by Hitt et al. (Advances in Pharmacology 40:137 (1997), submitted with the information disclosure statement dated April 24, 2002). This article discusses regions of adenoviral DNA that can be deleted in adenoviral vectors without loss of the ability to replicate or be packaged. For example, portions of the E1 and E3 regions can be deleted in first generation vectors. Thus, a nucleotide sequence encoding a modified adenoviral fiber protein which alters the tropism of the adenovirus vector can be inserted, for example, in one of these dispensable regions. The functions of these regions, as needed, can be provided in *trans*. In another example, a nucleotide sequence that mediates replication of an adenovirus in a transduced cell, including the nucleotide sequence encoding a modified adenoviral fiber protein, can be on the anti-parallel strand. Therefore, Applicants submit the skilled artisan could prepare a recombinant adenovirus vector with a nucleotide

sequence encoding a modified adenoviral fiber protein on the antiparallel strand, without undue experimentation.

Applicants therefore request the Examiner reconsider and withdraw this rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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MANDEL & ADRIANO

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: RECOMBINANT ADENOVIRAL VECTORS FOR CELL SPECIFIC INFECTION AND GENOME INTEGRATION AND EXPRESSING CHIMERIC FIBER PROTEINS

The specification of which

a. ☐ is attached hereto

b. ☒ was filed on November 30, 2001 as application serial no. 09/980,564 and was amended on December 2, 2003 (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/US00/15442 filed June 1, 2000 and as amended on September 12, 2000, September 10, 2001 (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (attached hereto).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☐ no such applications have been filed.

b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
PCT	PCT/US00/15442	01 June 2000	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby claim the benefit under Title 35, United States Code § 119(c) of any United States provisional application(s) listed below:

U.S. PROVISIONAL APPLICATION NUMBER	DATE OF FILING (Day, Month, Year)
60/137,213	01 June 1999
60/161,097	22 October 1999

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Samh B. Adriano
SaraLynn Mandel

Reg. No. 34,470
Reg. No. 31,853

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Mandel & Adriano to the contrary.

Please direct all correspondence in this case to Mandel & Adriano at the address indicated below:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Signature of Inventor 203:			Date: 9/28/2004	

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

- (1) prior art cited in search reports of a foreign patent office in a counterpart application, and
- (2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

- (1) It establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim; or
- (2) It refutes, or is inconsistent with, a position the applicant takes in:
 - (i) Opposing an argument of unpatentability relied on by the Office, or
 - (ii) Asserting an argument of patentability.

A *prima facie* case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

- (1) Each inventor named in the application;
- (2) Each attorney or agent who prepares or prosecutes the application; and
- (3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

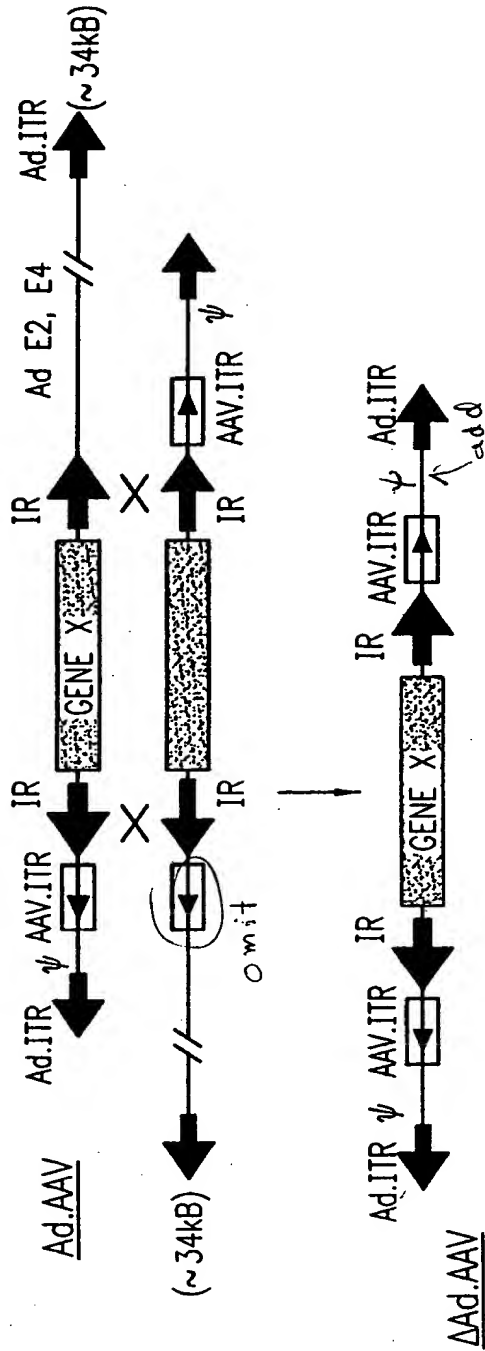


FIG. 17A

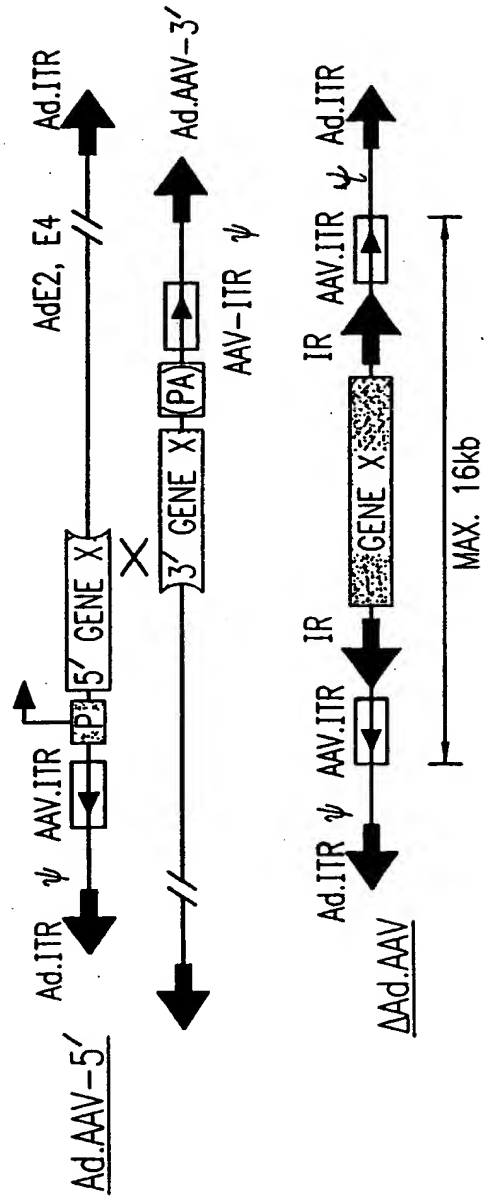


FIG. 17B